gfzf, the love that will tear us (Drosophila) apart

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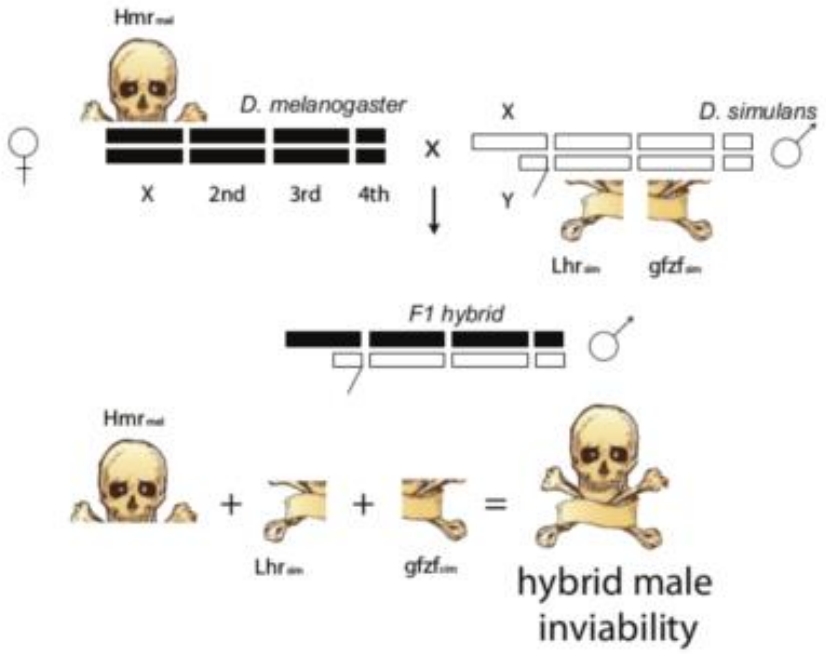

Image provided by Dr. Harmit Malik.

One of the longstanding questions in biology is how species become different from one another. Because the term "species" is operationally defined as a group of organisms that can produce fertile offspring, when two organisms from different species mate, the resulting offspring (hybrids) are either dead or sterile. This is also true in the fruit fly genus *Drosophila*, as it had been known for more than a century that crosses between *Drosophila melanogaster* females and males from its closest relative species, *Drosophila simulans*, lead to viable female hybrids but inviable male hybrids. Of note, hybrid males are born and undergo embryonic development but never reach adulthood. However, the genetic basis for this hybrid incompatibility remained unknown until two genes were identified in the past decade that when mutated, allowed hybrid males to survive. One was a *D. melanogaster* gene known as *Hybrid male rescue* (*Hmr*) and the other, *Lethal hybrid rescue* (*Lhr*), a *D. simulans* gene. However, while necessary, Hmr from *D. melanogaster* (Hmr^{mel}) and *Lhr* from *D.simulans* (Lhr^{sim}) are not sufficient for hybrid inviability as *D.melanogaster* males expressing both Hmr^{mel} and Lhr^{sim} are viable. These results suggest that there was at least another hybrid inviability gene present in *D.simulans*.

Because traditional genetic approaches have failed to identify the missing hybrid inviability gene from either experimental nor natural D. simulans populations, Drs. Nitin Phandnis and Harmit Malik (Basic Sciences Division) devised a genomics-based screen to identify such a gene. "We knew for decades that something like this gene ought to exist, and our approach finally allowed us to identify it", said Dr. Phadnis, a former post-doctoral fellow in the Malik Laboratory, who now leads his own research group at the University of Utah. This study, published in *Science*, began by painstakingly feeding 55,000 *D. simulans* adult males a chemical mutagen (ethyl methane sulfonate) and crossing these *en masse* to normal *D. melanogaster* females. Hybrids harboring mutations in the missing hybrid incompatibility gene were predicted to be viable and the authors were indeed able to recover six independent hybrid males, after sifting through more than 300,000 hybrid females. Because these males were sterile, the investigators performed whole-genome sequencing to pinpoint the causal mutation. While all six lines harbored between 600 and 1200 new mutations when compared to the non-mutagenized parental *D. simulans* strain, remarkably only one gene was mutated across all six males. This gene, with the unpronounceable name of *glutathione-S-transferase-containing FLYWICH zing finger protein* (*gfzf*), was shown to be the missing hybrid incompatibility gene as RNA interference of the *D.simulans gfzf* ($gfzf^{sim}$), but not its *D. melanogaster* counterpart ($gfzf^{mel}$), was sufficient to rescue the viability of hybrid males. Next, the authors hypothesized that the primary defect of $gfzf^{sim}$-mediated lethality was a defect in cell division as Gfzf is a known regulator of both normal cell division and cell cycle arrest upon DNA damage. They obtained two lines of evidence that supported their hypothesis. First, they knocked down $gfzf^{sim}$ specifically in proliferating cells of developing larvae, which was sufficient to rescue hybrid males. Second, the scientists observed cell proliferation directly with 5'ethynyl-2'deoxyuridine (EdU) labeling to monitor DNA synthesis in the larval nervous system, which showed that cell proliferation was restored in the "rescue" males (see figure). Taken together, these results suggest that the primary defect of hybrid males is cell proliferation in diploid tissues and that removing $gfzf^{sim}$ from stem and progenitor cells of the nervous system of male hybrids rescues their cell cycle arrest. In summary, this study identified an essential cell cycle regulator as a novel hybrid incompatibility gene in *Drosophila* and suggests that genes that control the checks and balances of the cell cycle are also involved in the evolution of reproductive isolation. Said Dr. Phadnis, "A big surprise is that the gene that makes fruit fly hybrids inviable – named gfzf – is a "cell cycle-regulation gene" or "cell cycle-checkpoint gene. Cancer biologists are interested in cell cycle checkpoints because you can get cancer when those go bad [and cells proliferate uncontrolled]. Biologists want to understand the machinery. This work shows that some of those components in the cell cycle policing machinery may be quickly changing".

Phadnis N, Baker EP, Cooper JC, Frizzell KA, Hsieh E, de la Cruz AFA, Shendure J, Kitzman JO, Malik HS. 2015. An essential cell cycle regulation gene causes hybrid inviability in *Drosophila*. *Science*. 350(6267):1552-5. doi: 10.1126/science.aac7504.

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